



General

Guideline Title

The role of radiotherapy in the management of patients with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline.

Bibliographic Source(s)

Ryken TC, Parney I, Buatti J, Kalkanis SN, Olson JJ. The role of radiotherapy in the management of patients with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. *J Neurooncol.* 2015 Dec;125(3):551-83. [104 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The rating schemes used for the strength of the evidence (Class I-III) and the levels of recommendations (Level I-III) are defined at the end of the "Major Recommendations" field.

Questions

1. What is the optimal role of external beam radiotherapy in the management of adult patients with newly diagnosed low grade glioma in terms of improving outcome (i.e., survival, complications, seizure control or other reported outcomes of interest)?
2. Which radiation strategies (dose, timing, fractionation, stereotactic radiation, brachytherapy, chemotherapy) improve outcomes compared to standard external beam radiation therapy in the initial management of low grade gliomas in adults?
3. Do specific factors (e.g., age, volume, extent of resection, genetic subtype) identify subgroups with better outcomes following radiation therapy than the general population of adults with newly diagnosed low grade gliomas?

Target Population

These recommendations apply to adults with newly diagnosed diffuse low grade glioma.

Recommendations

Outcomes in Adult Patients with Newly Diagnosed Low Grade Glioma Treated with Radiotherapy

- *Level I.* Radiotherapy is recommended in the management of newly diagnosed low grade glioma in adults to prolong progression free

survival, irrespective of extent of resection.

- *Level II.* Radiotherapy is recommended in the management of newly diagnosed low grade glioma in adults as an equivalent alternative to observation in preserving cognitive function, irrespective of extent of resection.
- *Level III.* Radiotherapy is recommended in the management of newly diagnosed low grade glioma in adults to improve seizure control in patients with epilepsy and subtotal resection.
- *Level III.* Radiotherapy is recommended in the management of newly diagnosed low grade glioma in adults to prolong overall survival in patients with subtotal resection.
- *Level III.* Consideration of the risk of radiation induced morbidity, including cognitive decline, imaging abnormalities, metabolic dysfunction and malignant transformation, is recommended when the delivery of radiotherapy is selected in the management of newly diagnosed low grade glioma in adults.

Strategies of Radiotherapy in Adult Patients with Newly Diagnosed Low Grade Glioma

- *Level I.* Lower dose radiotherapy is recommended as an equivalent alternative to higher dose immediate postoperative radiotherapy (45–50.4 vs. 59.4–64.8 Gy) in the management of newly diagnosed low grade glioma in adults with reduced toxicity.
- *Level III.* Delaying radiotherapy until recurrence or progression is recommended as an equivalent alternative to immediate postoperative radiotherapy in the management of newly diagnosed low grade glioma in adults but may result in shorter time to progression.
- *Level III.* The addition of chemotherapy to radiotherapy is not recommended over whole brain radiotherapy alone in the management of low grade glioma, as it provides no additional survival benefit.
- *Level III.* Limited-field radiotherapy is recommended over whole brain radiotherapy in the management of low grade glioma.
- *Level III.* Either stereotactic radiosurgery or brachytherapy are recommended as acceptable alternatives to external radiotherapy in selected patients.

Prognostic Factors in Adult Patients with Newly Diagnosed Low Grade Glioma Treated with Radiotherapy

- *Level II.* It is recommended that age greater than 40 years, astrocytic pathology, diameter greater than 6 cm, tumor crossing the midline and preoperative neurological deficit be considered as negative prognostic indicators when predicting overall survival in adult low grade glioma patients treated with radiotherapy.
- *Level II.* It is recommended that smaller tumor size, extent of surgical resection and higher mini-mental status exam be considered as positive prognostic indicators when predicting overall survival and progression free survival in patients in adult low grade glioma patients treated with radiotherapy.
- *Level III.* It is recommended that seizures at presentation, presence of oligodendroglial histological component and 1p19q deletion (along with additional relevant factors—see Table 1 in the original guideline document) be considered as positive prognostic indicators when predicting response to radiotherapy in adults with low grade gliomas.
- *Level III.* It is recommended that increasing age, decreasing performance status, decreasing cognition, presence of astrocytic histological component (along with additional relevant factors [see Tables 1 and 2 in the original guideline document]) be considered as negative prognostic indicators when predicting response to radiotherapy.

Definitions

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Evidence on Therapeutic Effectiveness and Levels of Recommendation

Evidence Classification	
Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g., case control and cohort studies)
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls
Levels of Recommendation	
Level 1	Generally accepted principles for patient management, which reflect a high degree of clinical certainty (usually this requires Class I evidence which directly addresses the clinical questions or overwhelming Class II evidence when circumstances preclude randomized clinical trials)
Level	Recommendations for patient management which reflect clinical certainty (usually this requires Class II evidence or a strong

2	consensus of class III evidence)	Evidence Classification
Level 3	Other strategies for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion)	

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Diffuse low grade glioma

Guideline Category

Management

Treatment

Clinical Specialty

Neurology

Oncology

Radiation Oncology

Intended Users

Physicians

Guideline Objective(s)

- To provide guidance for the use of radiation therapy for diffuse low grade gliomas based on the data present in the literature
- To evaluate the evidence on the impact of radiation therapy on disease control and survival in adult patients with low grade gliomas
- To make recommendations based on this evidence for the role of radiation therapy for the management of these patients

Target Population

Adults with newly diagnosed diffuse low grade glioma

Interventions and Practices Considered

1. External beam radiotherapy
2. Radiation strategies (dose, timing, fractionation, stereotactic radiation, brachytherapy, chemotherapy)
3. Assessment of specific prognostic factors (e.g., age, volume, extent of resection, genetic subtype) to identify subgroups with better outcomes following radiation therapy

Major Outcomes Considered

- Neurocognitive decline
- Radiation-induced changes
- Overall survival
- Progression-free survival
- Impact on seizure control
- Risk of malignant transformation
- Risk of cognitive decline
- Risk of hypothalamic dysfunction
- Morbidity
- Mortality

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

General Search Strategy

Literature Examination Approach

A wide-ranging literature search strategy was undertaken to identify all citations relevant to the management of low grade gliomas. The MEDLINE and EMBASE electronic databases were searched from 1990 through 2012, with additional data being gleaned from the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Registry, and Cochrane Database of Abstracts of Reviews of Effects. The search strategies used a combination of subheadings and text words with the specifics of this work being outlined in each guideline section. Reference lists of the publications chosen for full text review were also screened for potentially relevant studies.

Study Selection

The search of the bibliographic databases identified possibly relevant citations for a given topic and often these were large in number. The eligibility (inclusion/exclusion) criteria to screen the citations for each of the questions were determined ahead of time for each section by the writing group. At least two authors evaluated the titles and abstracts using the inclusion and exclusion criteria with broad interpretation of the criteria being used initially so as to maximize the likelihood of capturing pertinent information. Cases of disagreement about pertinence were resolved by a third author when needed. The full text articles of the selected abstracts were then collected and the same process of applying the eligibility criteria was carried out again with the more in depth information available. Articles that met the eligibility criteria were grouped according to the questions they addressed and used to create the evidence tables and scientific foundation sections. Reasons for exclusion for papers were also documented so as to be able to discuss pertinent problem citations in the scientific foundation as needed.

Specific Search Strategy for This Guideline

Literature Review

A broad search strategy was used due to the relative small number of studies on each specific topic. PubMed (National Library of Medicine, <http://www.ncbi.nlm.nih.gov>) was searched using Endnote (Thomson Reuters, Inc. <http://www.endnote.com>) according to the following strategy:

Low grade glioma OR Grade II glioma OR Grade II astrocytoma OR Grade II oligodendroglioma OR Grade II oligoastrocytoma AND radiotherapy NOT glioblastoma NOT anaplastic.

General Eligibility Criteria for Literature

This strategy noted yielded 1808 references. General eligibility criteria were then applied with the resultant narrowing of the publications to be considered as follows:

- Limiting to human yielded 1736 references.
- Limiting to English yielded 1495 references.
- Limiting to 1/1/1990–12/31/2012 yielded 1224 references.
- Limiting to adult 19+ years yielded 703 references.

Article Inclusion and Exclusion Criteria

Abstracts for the initial 703 references were then reviewed and selected based on their meeting the following predetermined criteria:

- Outcomes by grade/pathology could be clearly determined and included adult patients with diffuse Grade II gliomas, AND
- Outcomes following radiation therapy reported in at least 5 patients, AND
- Newly diagnosed patients

Number of Source Documents

Overall, 142 publications met the eligibility criteria and are included in the three Evidentiary Tables in the original guideline document.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Evidence on Therapeutic Effectiveness

Evidence Classification	
Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g., case control and cohort studies)
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

General Evidence Analysis

Quality Assessment and Statistical Methods

Articles that met the eligibility criteria were grouped according to the questions they addressed and used to create the evidence tables and scientific foundation sections. Reasons for exclusion for papers were also documented so as to be able to discuss pertinent problem citations in the scientific foundation as needed.

Studies which met the eligibility criteria were subject to more detailed scrutiny and had their data extracted by one reviewer and the extracted information was checked by one or more other reviewers. Evidence and summary tables, reporting the extracted study information and evidence classification, were generated for all of the included studies for each of the questions. Evidence tables were created with most recent data first and subsequent listings in retrograde chronological order. The table headings consisted of first author name and year, followed by a brief study description, chosen data class and conclusion. The authors were directed to craft the data in the tables in a succinct and fact filled manner so as to allow for understanding of the literature entry. The literature in the evidence tables was expanded upon in the scientific foundation of each section so as to emphasize important points supporting its classification and contribution to recommendations. The method by which this was accomplished is expanded upon in the Joint Guideline Committee Guideline Development Methodology document (see the "Availability of Companion Documents" field). Internal drafts of the tables and manuscripts were developed by sharing between writers electronically, by telephone and meetings. Summary and conclusion statements were included for each section, with comments on key issues for future investigation being added where pertinent.

Specific Evidence Analysis for This Guideline

Refer to the three Evidentiary Tables in the original guideline document for a description of studies included in the review and the data class assigned to each study. These included 54 publications focused on the optimal role of radiotherapy summarized in Evidentiary Table 1; 49 on radiotherapy strategy variation, summarized in Evidentiary Table 2; and 39 on prognostic factors summarized in Evidentiary Table 3.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Panel Development

Recognizing the serious nature of low grade gliomas along with the lack of consensus among various treatment options, the Joint Tumor Section of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) recommended that evidence-based guidelines be developed as a top priority, for the diagnosis, management and treatment of low grade glioma patients. The objectives of these guidelines are to establish the best evidence-based management of low grade gliomas in terms of imaging diagnosis, use of surgical biopsy and resection, assessment of tumor pathology, administration of systemic chemotherapy, and administration of radiation therapy. Because these tumors dependably recur or progress despite standard therapy, the Joint Tumor Section also recommended an evidence-based guideline be developed for progressive low grade gliomas and that information on promising emerging therapies be assessed in the same manner to determine the possible application of these findings.

Having identified the topical objectives, the Guidelines Committee of the Joint Tumor Section then recruited experts in the field from each of the parent organizations as lead writers of each section. These writers, in turn, recruited experts in non-neurosurgical specialties relevant to the field of management and therapy chosen. Writers were provided training on the method of guideline development as used in this guideline set by written methods and instructions. The senior authors and CNS Guidelines Manager then worked with them on a step by step basis to confirm that the methods were followed as the literature was collected, assessed and documents developed. When writers were approached and preliminarily agreed to participate they were asked to complete a formal conflict of interest questionnaire confirming the appropriateness of their participation. At that point they also agreed to report any new conflicts of interest that might develop during the writing process. In this manner a multidisciplinary panel of writers referred to as the Low Grade Glioma Guidelines Task Force was assembled, with significant administrative, logistical and analytical support from the national CNS Guidelines Committee. The method of this evidence-based clinical practice parameter guideline has been written in a manner to be as transparent as possible using published assessment criteria.

Topic Range of This Systematic Review and Clinical Practice Guideline

Having identified writing groups for each topic, the members designed questions to allow assessment of the literature in a manner that would provide guidance for management of low grade gliomas. These questions are presented at the beginning of each of the eight guideline chapters spanning the topics of imaging assessment, diagnostic biopsy, surgical resection, tumor evaluation by standard neuropathology and molecular techniques, radiation therapy, chemotherapy, emerging therapies and treatment of recurrent or progressive low grade gliomas.

Guideline Panel Consensus

Multidisciplinary writing groups were created for each section based on author expertise, in order to address each of the disciplines and particular

areas of therapy selected for these clinical guidelines. Each group was involved with literature selection, creation and editing of the evidence tables and scientific foundations for their specific section and discipline. Using this information, the writing groups then drafted the recommendations in answer to the questions formulated at the beginning of the process, culminating in the clinical practice guideline for their respective discipline. The draft guidelines were then circulated to the entire clinical guideline panel to allow for multidisciplinary feedback, discussion, and ultimately approval.

Rating Scheme for the Strength of the Recommendations

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Classification of Levels of Recommendation

Levels of Recommendation	
Level 1	Generally accepted principles for patient management, which reflect a high degree of clinical certainty (usually this requires Class I evidence which directly addresses the clinical questions or overwhelming Class II evidence when circumstances preclude randomized clinical trials)
Level 2	Recommendations for patient management which reflect clinical certainty (usually this requires Class II evidence or a strong consensus of class III evidence)
Level 3	Other strategies for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion)

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Approval Process

The completed evidence-based clinical practice guidelines for the management of low grade gliomas were presented to the Joint Guidelines Committee of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) for review. The reviewers for the Joint Guidelines Committee were vetted by the *Journal of Neuro-oncology* for suitability and expertise to serve as reviewers for the purposes of publication in that journal also. The final product was then approved and endorsed by the executive committees of both the AANS and CNS prior to publication in the *Journal of Neuro-oncology*.

The funding agencies (CNS Executive Committee and AANS/CNS Joint Tumor Section Executive Committee) were permitted to review these guidelines only after the Joint Guidelines Committee had completed its extensive review, critique and ultimate approval process; the funding groups then were limited to whether or not to endorse or reject this body of work but substantive changes were not allowed.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Class I data supports the level I recommendation that radiotherapy does extend progression free survival. Class I data also shows that lower dose radiotherapy provides this benefit, generally with less overall toxicity. Additionally, class III data provides information that limited field radiation may be used preferentially over whole brain radiation. Furthermore, study of radiosurgery and brachytherapy have provided class III data that these even more focused forms of radiation may be an acceptable alternative in selected populations. Class III data is presented suggesting that this therapy improves overall survival when complete resection cannot be accomplished at the time of diagnosis.
- There is concern over toxicity from the application of this modality early in management of this disease entity, but class II data supports a level II recommendation that preservation of cognitive function occurs in patients radiated soon after diagnosis that is equal to that of those that are simply observed till progression. Correlating with this is class III data that delaying radiation does not completely obviate its benefit but may be associated with a shorter time to progression after it is completed. Also there is class III evidence that suggests the use of radiation improves seizure control in individuals with newly diagnosed low grade gliomas.

Potential Harms

In spite of delineation of benefits from radiation, numerous class III studies have been published emphasizing the potential toxicity of radiation (see evidentiary tabled in the original guideline document). The managing physician must judge the potential benefits of this treatment modality against its possible downsides in an individualized assessment of the particular patient under consideration.

Qualifying Statements

Qualifying Statements

The information in these guidelines reflects the current state of knowledge at the time of completion. Each section is designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Ryken TC, Parney I, Buatti J, Kalkanis SN, Olson JJ. The role of radiotherapy in the management of patients with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. *J Neurooncol.* 2015 Dec;125(3):551-83. [104 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Dec

Guideline Developer(s)

American Association of Neurological Surgeons - Medical Specialty Society

Congress of Neurological Surgeons - Professional Association

Source(s) of Funding

These guidelines were funded exclusively by the Congress of Neurological Surgeons (CNS) Guidelines Committee, with no funding from any outside commercial sources. Development of this set of evidence-based clinical practice guidelines was editorially independent from the funding agencies.

Guideline Committee

American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee

Low Grade Glioma Guidelines Task Force

Composition of Group That Authored the Guideline

Authors: Timothy C. Ryken, Department of Neurosurgery, Kansas University Medical Center, Kansas City, KS, USA; Ian Parney, Department of Neurosurgery, Mayo Clinic, Rochester, MN, USA; John Buatti, Department of Radiation Oncology, University of Iowa Hospitals & Clinics, Iowa City, IA, USA; Steven N. Kalkanis, Department of Neurosurgery, Henry Ford Health System, Detroit, MI, USA; Jeffrey J. Olson, Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA, USA

Financial Disclosures/Conflicts of Interest

Conflict of Interest

Low Grade Glioma Guidelines Task Force members were required to report all possible conflicts of interest (COIs) prior to beginning work on the guideline, using the COI disclosure form of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of Task Force Members with possible conflicts and address this by restricting the writing

and reviewing privileges of that person to topics unrelated to the possible COIs.

Disclosures

Dr. Parney is a consultant for Agenus, Inc. Dr. Kalkanis is a consultant for Arbor and Varian. Dr. Olson is a consultant for the American Cancer Society; has received research funding from the National Cancer Institute, Genentech, and Millennium; and has received investigational drug provision from Merck.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the [Journal of Neuro-Oncology Web site](#) .

Availability of Companion Documents

The following are available:

- Rock J. Low grade glioma guidelines: foreword. J Neurooncol. 2015 Dec;125(3):447-8. Available from the [Journal of Neuro-Oncology Web site](#) .
- Olson JJ, Kalkanis SN, Ryken TC. Evidence-based clinical practice parameter guidelines for the treatment of adults with diffuse low grade glioma: introduction and methods. J Neurooncol. 2015 Dec;125(3):449-56. Available from the [Journal of Neuro-Oncology Web site](#) .
- Congress of Neurological Surgeons (CNS). Guideline development methodology: endorsed by the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the AANS/CNS Joint Guideline Committee. Schaumburg (IL): Congress of Neurological Surgeons (CNS); 2012 Feb. 12 p. [2 references]. Available from the [Congress of Neurological Surgeons Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 7, 2016. The information was not verified by the guideline developer.

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